REMARKS

I. Summary of the Office Action Mailed September 21, 2007

In the Office Action mailed September 21, 2007, the Examiner restated the previous Objection to the Drawings. Further, the Examiner rejected claims 1-10 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,716,638 ("Touitou") in view of U.S. Patent No. 6,509,005 ("Peart") and *"Airways Response to Aerosolized Delta-9-Tetrahydrocannabinol: Preliminary Report"* by Vachon *et al.* ("Vachon"). Further, the Examiner rejected claims 9-10 under 35 U.S.C. § 103(a) as being unpatentable over Touitou in view of Peart and Vachon, and further in view of U.S. Patent No. 5,258,336 ("LaMastro").

II. Status of the Claims

Claims 1-10 are currently pending.

III. Response to the Objection to the Drawings

In the Request for Continued Examination and Response to the Office Action of January 29, 2007, Applicant addressed the Examiner's specific objection to Figure 4 by noting the prior submission of a new Figure 4. The Examiner states that the current Objection to the Drawings is based on "multiple discrepancies." However, the exact nature and extent of these discrepancies is unclear to Applicant. In order to properly overcome the Examiner's objection, Applicant respectfully requests clarification as to the exact nature and extent of the objection. To this end, and to facilitate the prosecution of the current application, Applicant respectfully invites the Examiner to contact Applicant's representative at the number listed below.

IV. Response to the Rejections

A. It is Improper to Combine the Cited References

The Examiner relies primarily on the combination of Touitou and Peart to support an alleged finding of obviousness. Without conceding that the teachings of Touitou and Peart can actually be combined in a meaningful manner, the use of these references together is improper

for at least the reason that both references teach away from their combination. In addition, the modification of each reference according to the principles of the other renders the reference unsatisfactory for its intended purpose. Thus, any alleged combination of Toutitou and Peart is insufficient to show obviousness of the current claims.

1. The References Teach Away from Their Alleged Combination

A fundamental principal of Touitou is that the "ethosomal" compositions described therein must have a relatively high concentration of alcohol. (Touitou at Col. 1, line 64-Col. 2, line 3). More than just a requirement, high concentrations of alcohol are "crucial" to achieving the goal of high skin permeation for drug delivery. (Touitou at Col. 12, lines 2-4). In terms of actual percentages, a "relatively high concentration" according to Touitou means 20-50% for Ethanol, and 22-70% for Ethanol and Propylene Glycol. (Touitou at Col. 4, lines 22-24). In practice, for the two ethosomal compositions containing ethanol and THC, ethanol comprises nearly half of the solution: 49% for the THC 1 solution of Table 1, and 51.7% of the THC Ethosomal preparation in Example III. In addition to stating the necessity of using such high concentrations of alcohol, when distinguishing over the prior art Touitou also specifically discredits and discourages the use of concentrations lower than 20%. (Touitou at Col. 1, lines 51-64 (stating that "[t]he prior art teaches away from high concentrations of alcohol in the final liposomal preparations," and that in the prior art "[t]he alcohol, if present *is in low concentrations only, less than about 20% in the final product.*") (emphasis added)). Therefore, Touitou teaches compositions that critically rely upon high concentrations of alcohol, and specifically criticizes and discourages the use of lower concentrations of alcohol.

In contrast, Peart teaches only those compositions having concentrations preferably less than 20% and most preferably less than 15%. (Peart at Col. 5, lines 52-55). Although Peart suggests that the ratio of alcohol may be adjusted in order to create "appropriate sized droplets," he does not specifically discuss the use of ethanol concentrations greater than 20%. Instead,

Peart states that higher percentages of solvent cause the droplet size to increase. Moreover, Peart specifically discourages the use of ethanol contents greater than 20% when citing a study in which an ethanol content of about 23% resulted in droplets too large to be effectively inhaled. (Peart at Col. 5, lines 28-32). Thus, Peart teaches a composition that relies upon low concentrations of alcohol, and specifically criticizes and discourages the use of higher concentrations of alcohol.

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983). In examining an alleged combination of references, each prior art reference must be considered in its entirety (*i.e.*, as a whole), including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Because Touitou teaches the necessary use of higher concentrations of alcohol and glycol (greater than 22%), and because Peart teaches the use of low concentrations of alcohol (less than 20%), the two references inherently teach away from each other. Further, Touitou criticizes and discourages the use of low concentrations of alcohol, and specifically discourages the use of concentrations less than about 20%; Peart oppositely criticizes and discourages the use of high concentrations of alcohol. *Cf. In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004) (holding that a prior art's disclosure of more than one alternative does not constitute a teaching away where such disclosure does not criticize, discredit, or otherwise discourage the solution). Accordingly, the two references teach away from their alleged combination and cannot be combined.

2. The Proposed Modification of the References Renders Them Unsatisfactory

As noted above, Touitou teaches ethosomal compositions that are characterized by having a relatively high concentration of alcohol, where a high concentration of alcohol is crucial in enabling the high skin permeation of the ethosomal system. In contrast, Peart teaches a

composition having a low concentration of alcohol or solvent, where the low concentration of alcohol permits the formation of "respirable" particles or droplets.

If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then the references teach away from each other and cannot be combined. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Similarly' if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959). Modification of Touitou to have a concentration of ethanol less than 20%, as required by Peart, would destroy the principle operation of the Touitou; such a formulation would not be an ethosomal system, and would therefore lack the skin permeation enhancements that are the intended purpose of Toutiou. Similarly, by increasing the ethanol or solvent concentration of the composition of Peart to at or above 22%, as required by Touitou, any resulting aerosol would have droplets too large to be effectively inhaled, thereby defeating the purpose of Peart to create a stable aerosol-dispensable pharamceutical composition. Consequently, each reference modified according to the principles of the other renders the reference unable to achieve its intended purpose. Thus, both of these cited references further teach away from the alleged combination and cannot be combined.

B. Optimization Was Not Possible Through Routine Experimentation

The Examiner alleges it would have been obvious to optimize the mean mass media aerodynamic diameter of the composition of Touitou according to the guidance provided by Peart in order to provide a composition having the desired properties such as the desired T_{max}. (Office Action at Page 4, ¶3). However, the disclosures of Touitou and Peart indicate that optimization of the aeordynamic diameter of the composition could not have been achieved through routine experimentation.

Touitou and Peart disclose diametrically opposed means for achieving diameters less than 10 μm in size. While Touitou teaches that decreasing the concentration of ethanol decreases the particle size, Peart teaches the exact opposite (*i.e.*, that *increasing* the concentration of ethanol decreases the particle size). Peart specifically states that increasing the amount of organic solvent in the mixture causes the size of the particles to increase. (Peart at Col. 6, lines 16-20 ("However, higher percentages of solvent also cause droplet size to increase.")). To the contrary, Touitou specifically states that using a high alcoholic concentration favors the production of *smaller sized* populations. (Touitou at Col. 2, lines 26-2 ("High alcoholic (organic solvent) concentration favors the production of ethosomes in nm's range while high aqueous and phospholipid concentrations favor the formation of large size ethosomes")). Thus, according to the combined teachings of Touitou and Peart, a person should both *increase* the concentration of ethanol and *decrease* the concentration of ethanol in order to achieve particles sizes of less than 10 μm.

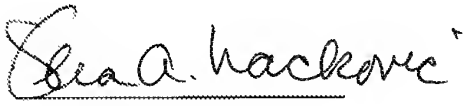
The Examiner states that where the general conditions of a claim is disclosed in the prior art, it is not inventive to discover the optimum ranges by routine experimentation. (Office Action at Page 4, ¶3 (citing *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). However, before the determination of the optimum or workable ranges of a variable can be characterized as routine experimentation, a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a *recognized* result. *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). In the present case, before the optimum or workable range of ethanol can be characterized as routine experimentation, it must be associated with achieving a *recognized* effect on particle diameters. Because Peart and Touitou each describe diametrically opposed means for achieving small particle diameters suitable for effective inhalation, it cannot be stated that the manipulation of ethanol concentration would have resulted in a recognized or known

effect on the particle size. Thus, such experimentation could not be characterized as routine, and it was not obvious to vary or optimize the mean mass aerodynamic diameter according to conditions set forth in either Peart or Touitou.

V. Conclusion

Because the Peart and Touitou references cannot be combined, a *prima facie* case of obviousness does not exist. Further, because these references illustrate the inherent ambiguity of the effect of ethanol concentration on particle size, it would not have been obvious to optimize the mean mass media aerodynamic diameter through routine optimization. All objections and rejections having been traversed. Therefore, Applicant submits that all claims are in condition for allowance and respectfully requests notice to that effect. Should the Examiner wish to discuss the case with the undersigned, the Examiner is invited to call the undersigned at 312-701-8115.

Respectfully Submitted,



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